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## **Hemobilia: Another Complication Associated with Anti-thrombotic Therapy**

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## Abstract

It is generally accepted that anti-thrombotic therapy increases the risk of gastrointestinal bleeding and concurrent therapy with a proton-pump inhibitor is a standard treatment for patients receiving aspirin. Thus, much attention has been paid to the prevention of gastrointestinal bleeding in such patients. However, it should be noted that patients treated with anti-thrombotic therapy always carry a risk of hemorrhage from any organs including the gastrointestinal tract. Here, we present a case with formation of a common bile duct stone caused by hemobilia associated with anti-thrombotic therapy. This case suggests that we need to bear in mind a possibility of intrabiliary hemorrhage as well as gastrointestinal bleeding in patients receiving anti-thrombotic therapy. Patients with the former complication show a variety of symptoms associated with liver abscess, cholangitis, pancreatitis, and duodenal bleeding.

## Introduction

Anti-thrombotic therapy is widely used for the prevention of heart attack and stroke [1 2, 3]. Patients treated with anti-coagulant and/or anti-platelet drugs sometimes suffer from gastrointestinal bleeding. Thus, anti-thrombotic therapy increases the risk of upper gastrointestinal bleeding and much attention has been paid to the prevention of gastrointestinal bleeding associated with anti-thrombotic therapy [1, 2, 3]. However, it should be noted that patients treated with such therapy always carry a risk of hemorrhage from any organs including the gastrointestinal tract. Hemobilia, which is defined as hemorrhage into the biliary tract, causes a variety of symptoms associated with gastrointestinal bleeding, liver abscess, cholangitis, and obstructive jaundice [4-6]. Causes of hemobilia include trauma, gallstones, aneurysma, tumor, and coagulopathy [4, 5]. Although spontaneous hemobilia may, like upper gastrointestinal bleeding, be caused by administration of anti-coagulant or anti-platelet drugs, little attention has been paid to the risk of hemobilia in patients treated with anti-thrombotic drugs. Here, we present a case with formation of a common bile duct (CBD) stone caused by hemobilia associated with anti-thrombotic therapy.

## Case Report

A 58-year-old man with a history of acute myocardial infarction (AMI) and diabetes mellitus presented to our hospital with fever and general fatigue. Blood examination revealed leukocytosis (11400 cells/mm<sup>3</sup>) and an elevated level of serum C-reactive protein (26.2 mg/dL; normal level<0.5). His serum hepatobiliary enzyme levels were also elevated (aspartate aminotransferase 53 IU/L; normal 13-33, alkaline phosphatase 461 IU/L; 129-241,  $\gamma$ -glutamyl transpeptidase 187 IU/L; 9-54). *Escherichia coli* was detected in his blood. Abdominal contrast-enhanced computed tomography, which was performed to detect the origin of the infection, revealed a tumor in segment 8 of the liver (Fig. 1) and a dilated CBD. The liver tumor consisted of a central hypo-dense area and peripheral areas with ring-like enhancements; these findings were consistent with those of pyogenic hepatic abscess [7]. Endoscopic

ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) revealed the presence of a narrow substance without acoustic shadowing at the bottom of the dilated CBD (Fig. 2A, B). This finding strongly suggested that the normal flow of bile was abrogated by the debris or stone in the CBD. Based on these data, the patient was diagnosed as septicemia due to liver abscess associated with debris or stone in the CBD. Although the patient had no history of gallbladder disease, EUS and MRCP revealed segmental wall thickening of fundal and body portions of the gallbladder, suggesting the presence of segmental and fundal type adenomyomatosis. The filling defect in the CBD was also detected using endoscopic retrograde cholangiography and a narrow-long fragile stone with dark brown color was endoscopically removed (Fig. 2C). The liver abscess resolved soon after the removal of the CBD stone, which suggested that this CBD stone was responsible for the liver abscess development.

Since the shape and color of this stone were different from those of the typical cholesterol and pigment stones, we analyzed this stone by using infrared absorption spectroscopy. Surprisingly, infrared absorption spectroscopy revealed that a major component (>98 %) of this stone was protein. The fact that this patient had been treated with anti-thrombotic therapy including systemic heparinization, after AMI, which occurred 6 months before admission led us to consider the possibility that clots originating from an intrabiliary hemorrhage caused by anti-thrombotic therapy became compact with increasing bile content to inhibit the normal bile flow. To verify this idea, we tried to detect the presence of serum proteins such as IgG in the protein extracts from this stone. We performed electrophoresis and immuno-blotting as described previously [8]. The presence of IgG light chain was confirmed by Coomassie blue staining of the blotted membrane when 56 µg of isolated proteins was applied to the gel (Fig. 3A). More importantly, immuno-blotting by using anti-human IgG antibody revealed the presence of both heavy and light IgG chains (Fig. 3B). Considering that gallstones usually do not contain a significant amount of human IgG, it is strongly suggested that the detected IgG originated from serum and that intraluminal clots caused by hemobilia became compact with increasing bile

content.

## Discussion

Upper gastrointestinal bleeding is often seen in patients treated by anti-thrombotic therapy [1, 2, 3]. In contrast, anti-thrombotic therapy causes intrabiliary hemorrhage in a very limited number of patients. Thus, it is likely that there is a trigger for the development of hemobilia in such patients. Such potential triggers include biliary inflammation and invasion of cancer cells into the biliary tract [4-6]. In this regard, spontaneous hemobilia is sometimes caused by overdoses of anti-platelet and/or coagulant drugs [5], which suggests the involvement of decreased coagulability in the development of hemobilia. Indeed, this patient had been treated with anti-thrombotic therapy including systemic heparinization. Further clinical analysis is required to determine the factors that increase the risk of intrabiliary hemorrhage in such patients.

An important finding from this case is that clots that remain in the bile duct may serve as a nidus for gallstone formation. We have proved that proteins isolated from the narrow substance in CBD contain a significant amount of IgG derived from serum. Thus, it is likely that the CBD substance causing liver abscess and dilatation of the bile duct originates from clots in this case. Therefore, formation of gallstone may be one of the late complications of hemobilia. Although acute biliary obstruction by clots sometimes causes fever, epigastralgia, and jaundice due to cholangitis, cholecystitis and pancreatitis at the onset of hemobilia [4, 5], similar symptoms can occur at a late phase as a result of stone formation. This idea is supported by the report on 2 cases of biliary calculi caused by hemobilia [9]. Given the fact that serum levels of  $\gamma$ -glutamyl transpeptidase in this case were elevated from two months before the admission, we speculate that clots in the bile duct had existed for more than two months in this case.

In conclusion, antithrombotic therapy may increase the risk of hepatobiliary diseases by causing hemobilia. We need to bear in mind a possibility of hemobilia as well as gastrointestinal bleeding in patients receiving

anti-thrombotic therapy.

## **Acknowledgements**

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## **Figure legends**

**Figure 1.** Abdominal computed tomography image showing the development of liver abscess in segment 8 (arrows).

**Figure 2.** (A) Magnetic resonance cholangiopancreatography image showing a narrow and long substance (arrows) at the bottom of the common bile duct (CBD). (B) Endoscopic ultrasonography image showing a narrow substance without acoustic shadowing at the bottom of the dilated CBD (arrows). (C) Endoscopic removal of a narrow-long fragile stone with dark brown color.

**Figure 3.** Protein extracts (14, 28, 56  $\mu$ g) isolated from the CBD stone was subjected to Coomassie blue staining (A) and immuno-blotting with anti-human IgG antibody (B). \*\* IgG heavy chain; \*, \*\*\* IgG light chain.

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